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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/713,808	11/14/2003	Dave S.B. Hoon	89212.0014	4483

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EXAMINER	
AEDER, SEAN E	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 09/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/713,808	HOON ET AL.	
	Examiner	Art Unit	
	Sean E. Aeder, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 July 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,10,11 and 31-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7, 10, 11, and 31-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

The Amendments and Remarks filed 7/3/06 in response to the Office Action of 3/24/06 are acknowledged and have been entered.

Claims 1-30 were pending.

Claims 8-9 and 12-30 have been cancelled by Applicant.

Claims 31-33 have been added by Applicant.

Claims 1-3 and 10 have been amended by Applicant.

Claims 1-7, 10, 11, and 31-33 are currently under examination.

The text of those sections of Title 35 U.S.C. code not included in this Office Action can be found in a prior Office Action.

The following Office Action contains NEW GROUNDS of rejections based on amendments.

Objections Withdrawn

The objections to claims 2 and 11 are withdrawn in view of amendments.

Rejections Withdrawn

The rejection of claims 1, 2, 4-7, 10, and 11 under 35 U.S.C. 112, second paragraph has been withdrawn in view of amendments. However, a new 35 U.S.C. 112, second paragraph rejection, based on amendments, is set-forth below.

The rejection of claims 1, 2, and 4-7, 10, and 11 under 35 U.S.C. 112, first paragraph has been withdrawn in view of amendments. However, a new 35 U.S.C. 112, first paragraph enablement rejection, based on amendments that changed the scope of claims 1, 2, and 4-7, 10, and 11, is set-forth below.

The rejections of claims 1, 2, 5, 10, and 11 under 35 U.S.C. 102 (b) are withdrawn in view of amendments.

The rejections of claims 1, 2, 5-7, 10, and 11 under 35 U.S.C. 103 (a) are withdrawn in view of amendments.

New Rejections Based on Amendments

35 USC § 112, second paragraph

Claims 1-7, 10, and 11 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1-7, 10, and 11 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. Claim 1 recites a method of predicting melanoma recurrence, disease-free survival, and overall survival of a melanoma patient by detecting levels of specific nucleic acid targets in a biological sample from said melanoma patient;

however, the claims do not indicate what kind of levels correlate with melanoma recurrence, disease-free survival, or overall survival. There are missing steps involving comparing a measured level from a sample to another level and correlating a specific type of comparison, or correlating a specific type of level from a sample, to a specific prognosis (melanoma recurrence, disease-free survival, or overall survival). See MPEP § 2172.01.

Claim 1-4, 6, 7, 10, and 11 are rejected because claim 1 recites a method of isolating nucleic acids from "a biological sample obtained from a melanoma patient, wherein the biological sample is associated with melanoma". It is not clear from the claims or the specification what biological samples are "associated with" melanoma. This renders the claim indefinite because the term "a biological sample obtained from a melanoma patient, wherein the biological sample is associated with melanoma" is not defined by the claim, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Given the above reasons, the metes and bounds of the claims cannot be determined.

35 USC § 112, first paragraph, Enablement Rejection

Claims 1-7, 10, and 11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for melanoma prognosis comprising isolating nucleic acid from sentinel lymph node samples and blood samples obtained from a melanoma patient and amplifying nucleic acid targets comprising

GalNAcT, PAX3, MART-1, MAGE-A3, and tyrosinase, wherein an increase in expression of said targets, as compared to expression of said targets in corresponding normal lymph tissue or normal blood samples, is indicative of an increase in metastatic melanoma recurrence, a decrease in metastatic-melanoma free survival, and a decrease in patient survival, does not reasonably provide enablement for a method for melanoma prognosis comprising isolating nucleic acid from just *any* biological sample from a melanoma patient deemed "associated with melanoma" and amplifying nucleic acid targets comprising GalNAcT, PAX3, MART-1, MAGE-A3, and tyrosinase, wherein *any* level of said targets is indicative of melanoma recurrence, survival without any kind of disease, and overall survival. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte* Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The instant claims are drawn to a method for melanoma prognosis comprising isolating nucleic acid from just *any* biological sample from a melanoma patient deemed "associated with melanoma" and amplifying nucleic acid targets comprising GalNAcT,

PAX3, MART-1, MAGE-A3, and tyrosinase, wherein *any* level of said targets is indicative of melanoma recurrence, survival without any kind of disease, and overall survival. The claims are further drawn to selecting treatment regimes based on said prognosis. It is noted that the claims broadly read on using any biological sample in the method, as it is not clear what would prevent a biological sample from being deemed "associated with melanoma". Further, the claims broadly read on any level of said targets being indicative of melanoma recurrence, survival without any kind of disease, and overall survival. Clearly, levels that are indicative of an increase in melanoma recurrence, a decrease in survival without any kind of disease, and a decrease in overall survival, for example, would not be indicated of a decrease in melanoma recurrence, an increase in survival without any kind of disease, and an increase in overall survival.

The specification discloses a method for melanoma prognosis comprising isolating nucleic acid from sentinel lymph node samples obtained from a melanoma patient and amplifying nucleic acid targets comprising GalNAcT, PAX3, MART-1, MAGE-A3, and tyrosinase, wherein an increase in expression of said targets, as compared to expression of said targets in corresponding normal lymph tissue is indicative of an increase in metastatic melanoma recurrence (Figure 4), a decrease in metastatic-melanoma free survival (Table 5), and a decrease in patient survival (Figure 5) (see pages 25-30, in particular). Further, the samples the specification *prophetically* discloses to use with the claimed method consist of paraffin-embedded (PE) melanoma tissues, frozen lymph nodes, and PE lymph nodes (page 6 lines 21-24, in particular).

Further, the specification provides no guidance, working examples, or exemplification demonstrating how detecting the expression of the target genes in a sample could be used to "select" any particular treatment regime from those commonly used to treat any metastatic melanoma.

Further, post-filing art teaches that the expression levels of a panel of marker genes including GalNAct and PAX3 in blood samples from melanoma patients are predictive of melanoma recurrence, disease-free survival, and overall survival (see page 8575 of Koyanagi et al (2005) J Clin Oncol 23(31):8057-8064).

The state of the prior art dictates that if an increase or decrease in expression of molecules such as nucleic acids encoding GalNAcT, PAX3, MART-1, MAGE-A3, and tyrosinase are to be used as surrogates for a diseased state, some disease state must be identified in some way with either an increase or a decrease in the expression of the molecules. There must be some expression pattern that would allow the markers to be used in a diagnostic manner. For example, Tockman et al (Cancer Res., 1992, 52:2711s-2718s) teach considerations necessary in bringing a cancer biomarker (intermediate end point marker) to successful clinical application. Tockman et al teaches that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials (see abstract). Early stage markers of carcinogenesis have clear biological plausibility as markers of preclinical cancer and if validated (emphasis added) can be used for population screening (p. 2713s, col 1). The

reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and *link* those marker results with subsequent histological confirmation of disease. This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate end point marker (p. 2714, see Biomarker Validation against Acknowledged Disease End Points). Clearly, prior to the successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials (p. 2716s, col 2). Therefore, absent evidence of the markers' expression including the correlation to a diseased state, one of skill in the art would not be able to predictably use the markers in any diagnostic setting without undue experimentation. In the instant case, it is apparent that an increase in expression of GalNAcT, PAX3, MART-1, MAGE-A3, and tyrosinase in sentinel lymph node samples and blood samples from melanoma patients, as compared to corresponding normal lymph tissue or normal blood samples, is indicative of an increase in metastatic melanoma recurrence, a decrease in metastatic-melanoma free survival, and a decrease in patient survival.

However, the level of unpredictability for prognosticating diseases is quite high. Since neither the specification nor the prior art provide evidence of a universal association between the claimed method and every type of sample, a practitioner

wishing to practice the claimed invention would be required to provide extensive experimentation to demonstrate such an association. Such experimentation would in itself be inventive.

One cannot extrapolate the teachings of the specification to the scope of the claims because the claims are broadly drawn to a method for melanoma prognosis comprising isolating nucleic acid from just *any* biological sample from a melanoma patient deemed "associated with melanoma" and amplifying nucleic acid targets comprising GalNAcT, PAX3, MART-1, MAGE-A3, and tyrosinase, wherein *any* level of said targets is indicative of melanoma recurrence, survival without any kind of disease, and overall survival, and Applicant has not enabled said method of prognosis because it has not been shown that *any* level of said targets in just any biological sample is indicative of melanoma recurrence, survival without any kind of disease, and overall survival. Further, the specification is not enabling for selecting any treatment regime based on any prognosis (claim 11), as the specification provides no guidance, working examples, or exemplification demonstrating how detecting the expression of said target genes in a sample could be used to "select" any particular treatment regime from those commonly used to treat any metastatic melanoma.

In view of the teachings above and the lack of guidance, workable examples and or exemplification in the specification, it would require undue experimentation by one of skill in the art to determine with any predictability, that the method would function as claimed.

Claim Rejections - 35 USC § 103

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 31-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Palmieri et al (March 2001, Journal of Clinical Oncology, 19(5):1437-1443) in view of Scholl et al (February 2001, Cancer Research, 61:823-826) and Kuo et al (February 1998, Clinical Cancer Research, 4:411-418).

Claim 31 is drawn to a method comprising obtaining a sentinel lymph node (SNL) sample from a melanoma patient, wherein the sample is histopathologically negative for melanoma cells; isolating nucleic acid from the sample; amplifying nucleic acid targets from a panel of marker genes, wherein the panel comprises GalNAct, PAX3, or both; and detecting the levels of the nucleic acid targets. Claim 32 is drawn to the method of claim 31, wherein the panel further comprises marker genes selected from the group consisting of MAGE-A3, MART-1, and Tyrosinase. Claim 33 is drawn to the method of claim 32, wherein the panel comprises a first combination of MAGE-A3, GalNAcT,

MART-1, and PAX3; or a second combination of Tyrosinase, MART-1, GalNAcT, and PAX3.

Palmieri et al teaches methods of detecting metastatic melanoma cells comprising isolating nucleic acids from sentinel lymph node samples obtained from a patient, using RT-PCR to isolated nucleic acids and amplify mRNA targets from a panel of marker genes comprising MART-1 and tyrosinase (pages 1438-1439, in particular). The methods taught by Palmieri et al comprise methods wherein the sentinel lymph node samples are histopathologically negative for melanoma cells (paragraph bridging the left and right columns of page 1438), wherein the histopathology is determined by hematoxylin and eosin staining and immunohistochemistry. Palmieri et al further teaches, and one of skill in the art would recognize, that multiple-marker assays are more sensitive and specific than single-marker assays in detecting metastatic melanoma cells (page 1441 right column, in particular).

Palmieri et al does not specifically teach methods of detecting metastatic melanoma cells comprising isolating nucleic acids from sentinel lymph node samples obtained from a patient, using RT-PCR to isolated nucleic acids and amplify mRNA targets from a panel of marker genes comprising MAGE-A3, GalNAcT and/or PAX3. However, these deficiencies are made up in the teachings of Scholl et al (February 2001, Cancer Research, 61:823-826) and Kuo et al (February 1998, Clinical Cancer Research, 4:411-418).

Scholl et al teaches methods of detecting metastatic melanoma cells comprising isolating nucleic acids from a biological sample obtained from a patient, amplifying

nucleic acid targets from a panel of marker genes comprising PAX3, MAGE-A3, and tyrosinase and detecting the presence or absence of the nucleic acid targets (Table 1 and Table 2, in particular).

Kuo et al teaches methods of detecting metastatic melanoma cells comprising isolating nucleic acids from a biological sample obtained from a patient, amplifying nucleic acid targets from a panel of marker genes comprising GalNAcT and detecting the presence or absence of GalNAcT (page 413 right column, in particular).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to detect metastatic melanoma cells comprising a method of isolating nucleic acids from histopathologically negative sentinel lymph node samples obtained from a patient, using RT-PCR to isolated nucleic acids and amplify mRNA targets from a panel of marker genes comprising MART-1 and tyrosinase as taught by Palmieri et al and also amplify any other genes associated with metastatic melanoma, such as those taught by Sholl et al (PAX3 and MAGE-A3) and Kuo et al (GalNAcT). Further, one would have been motivated to do so because multiple-marker assays are more sensitive and specific than single-marker assays in detecting metastatic melanoma cells. Further, one of skill in the art would have a reasonable expectation of success in performing the claimed method since detection of genes is well known and conventional in the art.

New Matter

Claims 1-4, 6, 7, 10, and 11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a NEW MATTER rejection.

Claim 1 recites "a biological sample obtained from a melanoma patient, wherein the biological sample is associated with melanoma". Descriptions of which biological samples are associated with melanoma are not found in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the invention was filed, had possession of the claimed invention.

Summary

No claim is allowed. Claims 1-7, 10, and 11 are rejected under 35 U.S.C. 112, first paragraph, but free of the prior art teaching a method for melanoma prognosis comprising isolating nucleic acid from a biological sample obtained from a melanoma patient wherein the biological sample is associated with melanoma; amplifying nucleic acid targets from a panel of marker genes, wherein the panel comprises GalNAcT, PAX3, or both; detecting the levels of the nucleic acid targets; and predicting melanoma recurrence, disease-free survival, overall survival, or a combination thereof, based on the levels of the nucleic acid targets. The closest prior art for claims 1-7, 10, and 11 is Kuo et al (February 1998, Clinical Cancer Research, 4:411-418); however, this

reference does not teach or suggest methods of predicting melanoma recurrence, disease-free survival, overall survival, or a combination thereof.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. ' 1.136(a). A shortened statutory period for response to this Final Action is set to expire three months from the date of this action. In the event a first response is filed within two months of the mailing date of this Final Action and the advisory action is not mailed until after the end of the three-month shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. '1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than six months from the date of this Final Action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean E. Aeder, Ph.D. whose telephone number is 571-272-8787. The examiner can normally be reached on M-F: 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SEA

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER